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Commentary

Cancer Immune Resistance Before and After Anti-PD Therapy

Artun Gursel*

Department of Immunology, Ihsan Dogramaci Bilkent University, Ankara, Turkey

DESCRIPTION

The main issue in cancer immunotherapy and oncology nowadays is overcoming resistance to anti-PD treatment. An understanding of the mechanisms underlying resistance should serve as the basis for strategy, rather than haphazardly combining existing medications and treatments. A few fundamental ideas are emerging and can be used to direct the treatment of cancer, even if our efforts to overcome resistance to anti-PD therapy are continuous and our understanding is far from complete.

It is obvious that the Tumor Microenvironment (TME) is the primary target of anti-PD treatment. To more clearly explain the dynamic and subtle changes taking place within the TME, more study is required. Therefore, collecting tissue is essential for researching resistance mechanisms. The immunological background of the TME in responders and nonresponders may only be distinguished through longitudinal biopsies performed before and after therapy. To investigate the changing immunological response within the TME, new technologies will be required. Recent developments in single-cell technologies have made it possible to identify important immune cells linked to anti-PD medication response. However, most research ignores the intricate architecture of the TME and focuses instead on a small number of populations of tumor-isolated cells that have been suspended.

With the use of multiplexed ion beam imaging, codetection by indexing (CODEX), imaging mass cytometry, and other single-cell spatial proteomics techniques, next-generation histology can achieve unparalleled spatial resolution of the TME's heterogeneity. Through histology-based transcriptomic platforms like digital spatial profiling and spatial transcriptomics, the spatial resolution of gene expression has also revealed fresh insights into the intricate tumor-immune interaction of malignancies. These new instruments could be used to find novel biomarkers linked to anti-PD therapy response and resistance mechanisms. Additionally, by examining the TME with single-cell spatial resolution, we may be able to identify various resistance mechanisms that work in concert inside the same tumor but are separated in time and space within microregions.

Predictive and prognostic biomarkers

Numerous signatures have been discovered since the first identification of immunological biomarkers linked to cancer prognosis, including T cell infiltration and B7-H1 expression. New biomarkers have appeared as a result of developments in computational biology and single-cell technologies, which stratify patients according to how well they respond to anti-PD therapy and offer crucial prognostic information. The usefulness of tumor mutational load as a biomarker of anti-PD therapy response has been questioned in light of subsequent investigations, despite the fact that it was initially discovered as a prognostic biomarker and predicted response to anti-PD therapy. The difficulty in finding a biomarker with therapeutic utility for the prediction of responses to anti-PD therapy is caused by TME heterogeneity between cancer types and within the same cancer. Given the complexity of immune evasion mechanisms, it is necessary to identify various biomarkers in order to choose the best immunotherapy to be employed either alone or in conjunction with anti-PD therapy.

Combination therapy

Combining anti-PD therapy with additional pharmacological targets to increase antitumor responses is a crucial strategy for overcoming resistance to the treatment. The most successful combo therapy is anti-CTLA-4 therapy. Despite having higher toxicities, it has proven beneficial in treating various tumors and is the gold standard of therapy for metastatic melanoma. Patients with melanoma generally survived longer for five years when CTLA-4 and PD-1 were both blocked. Severe systemic toxicity is one of the main disadvantages of anti-CTLA-4 combo therapy. Normalization cancer immunotherapy is the process of focusing on the local immune system's malfunction within the TME.

Normalization cancer immunotherapy

The classic cancer immunotherapy for normalization is anti-PD treatment. There is a critical need to recognize and target these pathways because the multiple immune evasion strategies adopted by malignancies imply the existence of additional crucial regulators in the TME. The development of

Correspondence to: Artun Gursel, Department of Immunology, Ihsan Dogramaci Bilkent University, Ankara, Turkey, E-mail: artun.gursel@ibg.edu.tr

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normalization cancer immunotherapies is guided by three ideas. Determine a local tumor immune escape mechanism that operates within the TME and is comparable to adaptive immune resistance in the first place. Second, focusing on immunological dysfunction in the TME specifically will reduce systemic damage. Finally, effective targeting of the local immune evasion mechanism should result in the elimination of cancer cells, reprogramming of an abnormal immune response into a normal antitumor immunological response, and promotion of tissue homeostasis. Although anti-PD treatment fits these normalization cancer immunotherapy concepts more closely than other immunotherapies, it still falls short. Patients using anti-PD medication may develop systemic side effects and insufficient cancer cell elimination. However, the tenets of normalizing cancer immunotherapy ought to act as an aspirational foundation for foreseeable treatments and sane clinical trial planning.